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FILE LAST UPDATED: 25 Apr 2003 (20030425/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr tot 182

L82 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS
AN 2003:174359 HCAPLUS
DN 138:201324
TI Coagulation assay reagents containing **lanthanides** and a **protein c** assay using such a **lanthanide**-containing reagent
IN Cutsforth, Gwyn A.; Mahan, Donald E.
PA Pharmanetics Incorporated, USA
SO U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM C12Q001-56
ICS C12N009-74
NCL 435013000; 435214000
CC 9-2 (**Biochemical Methods**)
Section cross-reference(s): 14
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003044871	A1	20030306	US 2001-938728	20010827
	WO 2003018741	A1	20030306	WO 2002-US3357	20020207
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
PRAI	US 2001-938728	A	20010827		
AB	A method, kit, system and reagent for performing coagulation assays with higher sensitivity and greater dynamic range is provided which involves the use of one or more metal compds. that interact with calcium binding sites in the blood coagulation cascade, particularly lanthanide compds., manganese compds. and				

ST magnesium compds. A Protein C reagent, kit,
and assay method is also provided using the same type of metal compds. to
provide greater detection sensitivity and dynamic range between samples.

IT coagulation assay reagent **lanthanide protein c**

IT **Proteins**

RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)

(C; coagulation assay reagents contg. **lanthanides**
and **protein c** assay using such a **lanthanide**
-contg. reagent)

IT **Blood analysis**

Blood coagulation

Blood plasma

Human

Magnetic particles

Test kits

(coagulation assay reagents contg. **lanthanides** and
protein c assay using such a **lanthanide**
-contg. reagent)

IT **Fibrins**

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(coagulation assay reagents contg. **lanthanides** and
protein c assay using such a **lanthanide**
-contg. reagent)

IT **Thrombomodulin**

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(**protein C activator**; coagulation assay reagents
contg. **lanthanides** and **protein c** assay
using such a **lanthanide**-contg. reagent)

IT **Venoms**

(snake; coagulation assay reagents contg. **lanthanides** and
protein c assay using such a **lanthanide**
-contg. reagent)

IT **7440-70-2, Calcium**, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(binding sites in blood coagulation cascade; coagulation assay reagents
contg. **lanthanides** and **protein c** assay
using such a **lanthanide**-contg. reagent)

IT **7439-91-0, Lanthanum**, biological studies

7439-95-4, Magnesium, biological studies

7439-96-5, Manganese, biological studies

7440-27-9, Terbium, biological studies **7440-53-1**
, **Europium**, biological studies **7440-54-2**,
Gadolinium, biological studies **9001-29-0**, Blood
coagulation factor X **9001-91-6**, **Plasminogen**
9002-01-1, **Streptokinase** **9002-05-5**,
Thromboplastin **9039-53-6**, **Urokinase**
10043-52-4, **Calcium chloride**, biological
studies **138757-15-0**

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(coagulation assay reagents contg. **lanthanides** and
protein c assay using such a **lanthanide**
-contg. reagent)

IT **7440-70-2, Calcium**, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(binding sites in blood coagulation cascade; coagulation assay reagents
contg. **lanthanides** and **protein c** assay
using such a **lanthanide**-contg. reagent)

RN **7440-70-2 HCPLUS**

CN **Calcium (8CI, 9CI) (CA INDEX NAME)**

Ca

IT 7439-91-0, Lanthanum, biological studies
7439-95-4, Magnesium, biological studies
7439-96-5, Manganese, biological studies
7440-27-9, Terbium, biological studies 7440-53-1
, Europium, biological studies 7440-54-2,
Gadolinium, biological studies 9001-29-0, Blood
coagulation factor X 9001-91-6, Plasminogen
9002-01-1, Streptokinase 9002-05-5,
Thromboplastin 9039-53-6, Urokinase
10043-52-4, Calcium chloride, biological
studies 138757-15-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(coagulation assay reagents contg. lanthanides and
protein c assay using such a lanthanide
-contg. reagent)
RN 7439-91-0 HCAPLUS
CN Lanthanum (8CI, 9CI) (CA INDEX NAME)

La

RN 7439-95-4 HCAPLUS
CN Magnesium (8CI, 9CI) (CA INDEX NAME)

Mg

RN 7439-96-5 HCAPLUS
CN Manganese (8CI, 9CI) (CA INDEX NAME)

Mn

RN 7440-27-9 HCAPLUS
CN Terbium (8CI, 9CI) (CA INDEX NAME)

Tb

RN 7440-53-1 HCAPLUS
CN Europium (8CI, 9CI) (CA INDEX NAME)

Eu

RN 7440-54-2 HCAPLUS
CN Gadolinium (8CI, 9CI) (CA INDEX NAME)

Gd

RN 9001-29-0 HCAPLUS
CN Blood-coagulation factor X (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9001-91-6 HCAPLUS
 CN Plasminogen (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9002-01-1 HCAPLUS
 CN Kinase (enzyme-activating), strepto- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9002-05-5 HCAPLUS
 CN Blood-coagulation factor Xa (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9039-53-6 HCAPLUS
 CN Kinase (enzyme-activating), uro- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 10043-52-4 HCAPLUS
 CN Calcium chloride (CaCl₂) (9CI) (CA INDEX NAME)

Cl-Ca-Cl

RN 138757-15-0 HCAPLUS
 CN Plasmin inhibitor, .alpha.2- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L82 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS
 AN 2001:228352 HCAPLUS
 DN 134:249240
 TI Method and constituent for processing blood for determining blood cell reaction
 IN Nagai, Hiroyuki
 PA Asahi Chemical Industry Co., Ltd., Japan
 SO Jpn. Kokai Tokkyo Koho, 10 pp.
 CODEN: JKXXAF
 DT Patent
 LA Japanese
 IC ICM G01N033-48
 ICS G01N033-48; A61B005-15
 CC 9-16 (Biochemical Methods)
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2001083144	A2	20010330	JP 1999-256245	19990909
PRAI	JP 1999-256245		19990909		
AB	A method is provided for processing blood so as to det. a blood cell reaction (e.g., mediator sepn. reaction from blood cell) with an excellent reproducibility and a low cost without sepg. the blood cell. The blood cell reaction is performed upon adding to a blood sample a chelating agent (e.g., EDTA, citric acid, oxalic acid), an anticoagulant without a chelating ability (e.g., heparin, plasmin, proteinase, azo dye, hirudin, dicumarol, thrombomodulin , antibody to anticoagulant, anticoagulant-binding receptor) and a metal salt (e.g., chloride, sulfate, carbonate, nitrate, phosphate) capable of eluting a divalent cation (e.g., Ca ²⁺ , Mg ²⁺ , Mn ²⁺ , Zn ²⁺ , Cd ²⁺ , Cu ²⁺) in an aq. medium. A reagent constituent used for this method is also claimed. The sepn. reaction of an mediator (e.g, histamine, leukotriene, platelet activating factor, cytokine) from blood cell was detd. with an excellent reproducibility using blood samples processed by this method.				

ST chelating agent anticoagulant metal blood analysis; blood cell mediator
hystamine leukotriene cytokine

IT Receptors
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(anticoagulant-binding; method and constituent for processing blood for
detg. blood cell reaction)

IT Cations
(divalent; method and constituent for processing blood for detg. blood
cell reaction)

IT Anticoagulants

Azo dyes

Blood
Blood analysis

Blood cell

Chelating agents

Sample preparation
(method and constituent for processing blood for detg. blood cell
reaction)

IT Cytokines

Leukotrienes
RL: ANT (Analyte); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell
reaction)

IT Carbonates, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell
reaction)

IT Chlorides, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell
reaction)

IT Nitrates, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell
reaction)

IT Phosphates, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell
reaction)

IT Sulfates, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell
reaction)

IT **Thrombomodulin**
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell
reaction)

IT Antibodies
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(to anticoagulant; method and constituent for processing blood for
detg. blood cell reaction)

IT 51-45-6, Histamine, analysis 65154-06-5, Platelet-activating
factor
RL: ANT (Analyte); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell
reaction)

IT 643-79-8, o-Phthalaldehyde
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(method and constituent for processing blood for detg. blood cell
reaction)

IT 60-00-4, EDTA, analysis 77-92-9, Citric acid, analysis 139-33-3
144-62-7, Oxalic acid, analysis 471-34-1, Calcium carbonate,
analysis 7439-95-4, Magnesium, analysis

7439-96-5, Manganese, analysis **7440-43-9**,
 Cadmium, analysis **7440-50-8**, Copper, analysis **7440-66-6**
 , Zinc, analysis **7440-70-2**, Calcium, analysis **7773-01-5**
 , **Manganese chloride** **7778-18-9**, Calcium sulfate
7786-30-3, **Magnesium chloride**, analysis **8001-27-2**,
 Hirudin **9001-90-5**, Plasmin **9001-92-7**, Proteinase
9002-04-4, Thrombin **9005-49-6**, Heparin, analysis **9041-08-1**,
 Sodium heparin **10043-52-4**, Calcium chloride, analysis
 RL: ARU (Analytical role, unclassified); ANST (Analytical study)
 (method and constituent for processing blood for detg. blood cell
 reaction)

IT **65154-06-5**, Platelet-activating factor
 RL: ANT (Analyte); ANST (Analytical study)
 (method and constituent for processing blood for detg. blood cell
 reaction)

RN **65154-06-5** HCPLUS

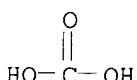
CN Blood platelet-activating factor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **471-34-1**, Calcium carbonate, analysis **7439-95-4**,
Magnesium, analysis **7439-96-5**, **Manganese**,
 analysis **7440-43-9**, Cadmium, analysis **7440-50-8**,
 Copper, analysis **7440-66-6**, Zinc, analysis **7440-70-2**,
 Calcium, analysis **7773-01-5**, **Manganese chloride**
7778-18-9, Calcium sulfate **7786-30-3**, **Magnesium**
 chloride, analysis **9001-90-5**, Plasmin **9002-04-4**,
 Thrombin **10043-52-4**, Calcium chloride, analysis
 RL: ARU (Analytical role, unclassified); ANST (Analytical study)
 (method and constituent for processing blood for detg. blood cell
 reaction)

RN **471-34-1** HCPLUS

CN Carbonic acid calcium salt (1:1) (8CI, 9CI) (CA INDEX NAME)



Ca

RN **7439-95-4** HCPLUS
 CN Magnesium (8CI, 9CI) (CA INDEX NAME)

Mg

RN **7439-96-5** HCPLUS
 CN Manganese (8CI, 9CI) (CA INDEX NAME)

Mn

RN **7440-43-9** HCPLUS
 CN Cadmium (8CI, 9CI) (CA INDEX NAME)

Cd

RN 7440-50-8 HCAPLUS
CN Copper (7CI, 8CI, 9CI) (CA INDEX NAME)

Cu

RN 7440-66-6 HCAPLUS
CN Zinc (7CI, 8CI, 9CI) (CA INDEX NAME)

Zn

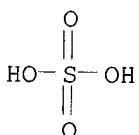
RN 7440-70-2 HCAPLUS
CN Calcium (8CI, 9CI) (CA INDEX NAME)

Ca

RN 7773-01-5 HCAPLUS
CN Manganese chloride (MnCl₂) (8CI, 9CI) (CA INDEX NAME)

Cl—Mn—Cl

RN 7778-18-9 HCAPLUS
CN Sulfuric acid, calcium salt (1:1) (8CI, 9CI) (CA INDEX NAME)



Ca

RN 7786-30-3 HCAPLUS
CN Magnesium chloride (MgCl₂) (9CI) (CA INDEX NAME)

Cl—Mg—Cl

RN 9001-90-5 HCAPLUS
CN Plasmin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9002-04-4 HCAPLUS
CN Thrombin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 10043-52-4 HCAPLUS
CN Calcium chloride (CaCl₂) (9CI) (CA INDEX NAME)

Cl-Ca-Cl

L82 ANSWER 3 OF 3 HCPLUS COPYRIGHT 2003 ACS
 AN 1999:614172 HCPLUS
DN 131:225815
 TI Screening for blood coagulation defects using metal ions
 IN Rosen, Bert Steffen; Hall, Christina Maria Yvonne
 PA Chromogenix AB, Swed.
 SO PCT Int. Appl., 67 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM C12Q001-56
 ICS G01N033-86
 CC 9-5 (Biochemical Methods)
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9947699	A1	19990923	WO 1999-EP1599	19990311
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 947585	A1	19991006	EP 1998-105043	19980319
	EP 947585	B1	20010725		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AT 203567	E	20010815	AT 1998-105043	19980319
	ES 2162361	T3	20011216	ES 1998-105043	19980319
	CA 2334935	AA	19990923	CA 1999-2334935	19990311
	AU 9930339	A1	19991011	AU 1999-30339	19990311
	US 6395501	B1	20020528	US 1999-273413	19990319
	US 2002115127	A1	20020822	US 2002-50441	20020116
PRAI	EP 1998-105043	A	19980319		
	WO 1999-EP1599	W	19990311		
	US 1999-273413	A1	19990319		
AB	An in vitro photometric method for qual. screening and quant. detn. of the functional activity of components of the Protein C anticoagulant pathway of blood coagulation, comprising measuring the conversion rate of an exogenous substrate by an enzyme, the activity of which is related to the Protein C anticoagulant activity, in a blood sample of a human comprising coagulation factors and said exogenous substrate after at least partial activation of coagulation through the intrinsic, extrinsic or common pathway and triggering coagulation by adding calcium ions; and comparing said conversion rate with the conversion rate of a normal human blood sample detd. in the same way, comprises adding further metal(s) ions to said sample. Kits and reagents for use in the method are also disclosed. By including manganese and magnesium ions with the calcium ions in a reaction system for the detn. of Protein C activity, a strong enhancement of the anticoagulant activity was obtained.				
ST	blood coagulation defect screening metal ion; protein C blood assay manganese magnesium ion				
IT	Chromophores Fluorescent substances Luminescent substances (as leaving group on enzyme substrate; screening for blood coagulation defects using metal ions)				

IT Metals, biological studies
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(divalent ions; screening for blood coagulation defects using metal ions)

IT Brain
Egg yolk
Placenta
Platelet (blood)
Soybean (Glycine max)
(phospholipids of; screening for blood coagulation defects using metal ions)

IT Fibrins
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(polymn. inhibitor; screening for blood coagulation defects using metal ions)

IT Blood-coagulation factors
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(protein S; screening for blood coagulation defects using metal ions)

IT **Blood analysis**
Blood coagulation
Photometry
Test kits
(screening for blood coagulation defects using metal ions)

IT Enzymes, biological studies
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT Collagens, biological studies
Kaolin, biological studies
Phosphatidylcholines, biological studies
Phosphatidylserines
Phospholipids, biological studies
Reagents
Sphingomyelins
Thrombomodulin
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT Blood-coagulation factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT Vipera russelli
(snake venom enzyme of; screening for blood coagulation defects using metal ions)

IT Agkistrodon
Agkistrodon contortrix contortrix
(snake venom enzymes of; screening for blood coagulation defects using metal ions)

IT Venoms
(snake, enzymes of; screening for blood coagulation defects using metal ions)

IT 67869-62-9
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical

study); BIOL (Biological study); PROC (Process); USES (Uses)
 (as fibrin polymn. inhibitor; screening for blood coagulation defects
 using metal ions)

IT 91-64-5D, Coumarin, derivs. 100-01-6D, p-Nitroaniline, derivs.
 3682-14-2D, Isoluminol, derivs. 25168-10-9D, Naphthylamine, derivs.
 RL: ARG (Analytical reagent use); BPR (Biological process); BSU
 (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical
 study); BIOL (Biological study); PROC (Process); USES (Uses)
 (as leaving group on enzyme substrate; screening for blood coagulation
 defects using metal ions)

IT 60457-00-3, S-2222 83160-48-9, CBS 31.39 88803-90-1, Spectrozyme Xa
 133943-48-3, S-2765
 RL: ARG (Analytical reagent use); BPR (Biological process); BSU
 (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical
 study); BIOL (Biological study); PROC (Process); USES (Uses)
 (as photometric substrate for Factor Xa; screening for blood
 coagulation defects using metal ions)

IT 36335-67-8, S-2846 62354-65-8, S-2238 72194-57-1, S-2366 88793-93-5,
 Spectrozyme TH 106775-37-5, CBS 34.47 244085-35-6, S 2796
 RL: ARG (Analytical reagent use); BPR (Biological process); BSU
 (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical
 study); BIOL (Biological study); PROC (Process); USES (Uses)
 (as photometric substrate for thrombin; screening for blood coagulation
 defects using metal ions)

IT 60202-16-6, Protein C
 RL: ANT (Analyte); ARG (Analytical reagent use); BAC (Biological activity
 or effector, except adverse); BPR (Biological process); BSU (Biological
 study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL
 (Biological study); PROC (Process); USES (Uses)
 (screening for blood coagulation defects using metal ions)

IT 9001-24-5D, Blood-coagulation factor V, mutants
 RL: ANT (Analyte); BAC (Biological activity or effector, except adverse);
 BPR (Biological process); BSU (Biological study, unclassified); THU
 (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC
 (Process); USES (Uses)
 (screening for blood coagulation defects using metal ions)

IT 9002-04-4, Thrombin 9002-05-5, Blood factor Xa
 RL: ARG (Analytical reagent use); BAC (Biological activity or effector,
 except adverse); BPR (Biological process); BSU (Biological study,
 unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL
 (Biological study); PROC (Process); USES (Uses)
 (screening for blood coagulation defects using metal ions)

IT 9001-24-5, Blood-coagulation factor V 9001-25-6,
 Blood-coagulation factor VII 9001-26-7, Prothrombin
 9001-28-9, Factor IX 9001-29-0, Factor X
 42617-41-4, Activated Protein C 65312-43-8, Factor VIIa
 65522-14-7, Factor Va 72162-96-0, Thromboplastin
 72175-66-7, Blood-coagulation Factor VIIIa 113189-02-9,
 Factor VIII
 RL: ARG (Analytical reagent use); BPR (Biological process); BSU
 (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical
 study); BIOL (Biological study); PROC (Process); USES (Uses)
 (screening for blood coagulation defects using metal ions)

IT 476-66-4, Ellagic acid 7631-86-9, Silica, biological studies
 7773-01-5, Manganese chloride 7785-87-7,
 Manganese sulfate 7786-30-3, Magnesium
 chloride, biological studies 10043-52-4, Calcium chloride,
 biological studies 10377-60-3, Magnesium nitrate
 14127-61-8, Calcium ion, biological studies 14701-22-5,
 Ni²⁺, biological studies 15158-11-9, Cu²⁺, biological studies
 16397-91-4, Mn²⁺, biological studies 17493-86-6, Cuprous
 ion, biological studies 22537-22-0, Mg²⁺, biological studies
 22537-39-9, Sr²⁺, biological studies 23713-49-7, Zn²⁺,

biological studies 37203-61-5, Blood-coagulation Factor XIa
37203-62-6, Blood-coagulation Factor XIIa 37316-87-3,
 Blood-coagulation Factor IXa 69670-93-5, Cephotest 110617-83-9, Protac
 C

RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
 (screening for blood coagulation defects using metal ions)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Bartl Knut; US 5001069 A 1991 HCPLUS
- (2) Baxter Diagnostics Inc; EP 0567636 A 1993 HCPLUS
- (3) Baxter Diagnostics Inc; WO 9310262 A 1993 HCPLUS
- (4) Bernardo, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1993, V268(17), P12468 HCPLUS
- (5) Butenas, S; BIOCHEMISTRY 1994, V33(11), P3449 HCPLUS
- (6) Heeb, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1991, V266(26), P17606 HCPLUS
- (7) Liebman, H; JOURNAL OF BIOLOGICAL CHEMISTRY 1987, V262(16), P7605 HCPLUS
- (8) Pedersen, A; THROMBOSIS AND HAEMOSTASIS 1991, V65(5), P528 HCPLUS
- (9) Proksch, G; US 5055412 A 1991 HCPLUS
- (10) Sekiya, F; JOURNAL OF BIOLOGICAL CHEMISTRY 1995, V270(24), P14325 HCPLUS
- (11) Shore, J; BIOCHEMISTRY 1987, V26(8), P2250 HCPLUS
- (12) Speck, R; US 5637452 A 1997 HCPLUS

IT 60202-16-6, Protein C

RL: ANT (Analyte); ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
 (screening for blood coagulation defects using metal ions)

RN 60202-16-6 HCPLUS

CN Blood-coagulation factor XIV (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9001-24-5D, Blood-coagulation factor V, mutants

RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
 (screening for blood coagulation defects using metal ions)

RN 9001-24-5 HCPLUS

CN Blood-coagulation factor V (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9002-04-4, Thrombin 9002-05-5, Blood factor Xa

RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
 (screening for blood coagulation defects using metal ions)

RN 9002-04-4 HCPLUS

CN Thrombin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9002-05-5 HCPLUS

CN Blood-coagulation factor Xa (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9001-24-5, Blood-coagulation factor V 9001-25-6,

Blood-coagulation factor VII 9001-26-7, Prothrombin

9001-28-9, Factor IX 9001-29-0, Factor X 42617-41-4

, Activated Protein C 65312-43-8, Factor VIIa

65522-14-7, Factor Va 72162-96-0, Thromboplastin

72175-66-7, Blood-coagulation Factor VIIIa 113189-02-9,

Factor VIII

RL: ARG (Analytical reagent use); BPR (Biological process); BSU

(Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(screening for blood coagulation defects using metal ions)

RN 9001-24-5 HCAPLUS
CN Blood-coagulation factor V (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9001-25-6 HCAPLUS
CN Blood-coagulation factor VII (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9001-26-7 HCAPLUS
CN Blood-coagulation factor II (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9001-28-9 HCAPLUS
CN Blood-coagulation factor IX (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9001-29-0 HCAPLUS
CN Blood-coagulation factor X (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 42617-41-4 HCAPLUS
CN Blood-coagulation factor XIVA (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 65312-43-8 HCAPLUS
CN Blood-coagulation factor VIIa (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 65522-14-7 HCAPLUS
CN Blood-coagulation factor Va (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 72162-96-0 HCAPLUS
CN Prothrombinase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 72175-66-7 HCAPLUS
CN Blood-coagulation factor VIIIA, procoagulant (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 113189-02-9 HCAPLUS
CN Blood-coagulation factor VIII, procoagulant (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 7773-01-5, Manganese chloride 7785-87-7,
Manganese sulfate 7786-30-3, Magnesium
chloride, biological studies 10043-52-4, Calcium chloride,
biological studies 10377-60-3, Magnesium nitrate
14127-61-8, Calcium ion, biological studies 14701-22-5,
Ni²⁺, biological studies 15158-11-9, Cu²⁺, biological studies
16397-91-4, Mn²⁺, biological studies 17493-86-6, Cuprous
ion, biological studies 22537-22-0, Mg²⁺, biological studies
22537-39-9, Sr²⁺, biological studies 23713-49-7, Zn²⁺,
biological studies 37203-61-5, Blood-coagulation Factor XIa
37203-62-6, Blood-coagulation Factor XIIa 37316-87-3,
Blood-coagulation Factor IXa
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical
study); BIOL (Biological study); USES (Uses)
(screening for blood coagulation defects using metal ions)

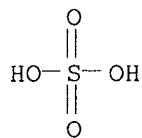
RN 7773-01-5 HCAPLUS

CN Manganese chloride (MnCl₂) (8CI, 9CI) (CA INDEX NAME)

Cl—Mn—Cl

RN 7785-87-7 HCPLUS

CN Sulfuric acid, manganese(2+) salt (1:1) (8CI, 9CI) (CA INDEX NAME)



Mn (II)

RN 7786-30-3 HCPLUS

CN Magnesium chloride (MgCl₂) (9CI) (CA INDEX NAME)

Cl—Mg—Cl

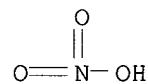
RN 10043-52-4 HCPLUS

CN Calcium chloride (CaCl₂) (9CI) (CA INDEX NAME)

Cl—Ca—Cl

RN 10377-60-3 HCPLUS

CN Nitric acid, magnesium salt (8CI, 9CI) (CA INDEX NAME)



1/2 Mg

RN 14127-61-8 HCPLUS

CN Calcium, ion (Ca²⁺) (8CI, 9CI) (CA INDEX NAME)

Ca²⁺

RN 14701-22-5 HCPLUS

CN Nickel, ion (Ni²⁺) (8CI, 9CI) (CA INDEX NAME)

Ni²⁺

RN 15158-11-9 HCPLUS

CN Copper, ion (Cu²⁺) (8CI, 9CI) (CA INDEX NAME)

Cu²⁺

RN 16397-91-4 HCPLUS
CN Manganese, ion (Mn²⁺) (8CI, 9CI) (CA INDEX NAME)

Mn²⁺

RN 17493-86-6 HCPLUS
CN Copper, ion (Cu¹⁺) (8CI, 9CI) (CA INDEX NAME)

Cu⁺

RN 22537-22-0 HCPLUS
CN Magnesium, ion (Mg²⁺) (8CI, 9CI) (CA INDEX NAME)

Mg²⁺

RN 22537-39-9 HCPLUS
CN Strontium, ion (Sr²⁺) (8CI, 9CI) (CA INDEX NAME)

Sr²⁺

RN 23713-49-7 HCPLUS
CN Zinc, ion (Zn²⁺) (8CI, 9CI) (CA INDEX NAME)

Zn²⁺

RN 37203-61-5 HCPLUS
CN Blood-coagulation factor XIa (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 37203-62-6 HCPLUS
CN Blood-coagulation factor XIIa (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 37316-87-3 HCPLUS
CN Blood-coagulation factor IXa (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> fil wpix
FILE 'WPIX' ENTERED AT 15:16:12 ON 26 APR 2003
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FILE LAST UPDATED: 10 APR 2003 <20030410/UP>
MOST RECENT DERWENT UPDATE: 200324 <200324/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

Due to data production problems the WPI file had to be reset to update 200324.
 SDIs for update 24 will be rerun.
 The previous SDI run for 24 has been credited.
 Also answer sets created after April 10 may at least temporarily be affected and hence partially invalid.

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS <<<
 >>> SLART (Simultaneous Left and Right Truncation) is now available in the /ABEX field. An additional search field /BIX is also provided which comprises both /BI and /ABEX <<<
 >>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<
 >>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
 SEE <http://www.derwent.com/dwpi/updates/dwpicov/index.html> <<<
 >>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
 PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<
 >>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d all abeq tech abex tot

L30 ANSWER 1 OF 7 WPIX (C) 2003 THOMSON DERWENT
 AN 2002-444491 [47] WPIX
 DNC C2002-126626
 TI Assessing platelet/leukocyte interaction caused by e.g. inflammation by contacting a whole blood or blood-derived sample with a solid phase stimulus having bound to its surface a ligand for binding platelets or leukocytes.
 DC B04
 IN MAHAN, D E; STEWART, M W
 PA (PHAR-N) PHARMANETICS INC
 CYC 98
 PI WO 2002039949 A2 20020523 (200247)* EN 39p A61K000-00
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
 RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZM ZW
 AU 2002033923 A 20020527 (200261) A61K000-00
 ADT WO 2002039949 A2 WO 2001-US42946 20011115; AU 2002033923 A AU 2002-33923
 20011115
 FDT AU 2002033923 A Based on WO 200239949
 PRAI US 2000-712165 20001115
 IC ICM A61K000-00
 AB WO 200239949 A UPAB: 20020725
 NOVELTY - Assessing (A1) platelet/leukocyte interaction involves:
 (a) contacting a whole blood or blood-derived sample with a solid-phase stimulus; and
 (b) detecting the formation of at least one platelet/leukocyte/solid-phase stimulus complex.
 The solid-phase stimulus comprises microparticles and has bound to its surface a ligand (L1) selective for binding platelets or leukocytes.
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
 (1) a platelet/leukocyte interaction assay reagent (I) comprising a mixture of magnetic and non-magnetic particles, and a leukocyte marker.

The magnetic or non-magnetic particles have bound to their outer surface a first ligand (L2) or a second ligand (L3) respectively having an affinity for direct interaction with blood platelets;

(2) a platelet/leukocyte interaction assay réagent (II) comprising a mixture of magnetic and non-magnetic particles where either the magnetic or non-magnetic particles have bound to their outer surface a first ligand having affinity for direct interaction with blood platelets and the other of the magnetic or non-magnetic particles have bound to their outer surface a second ligand having affinity for direct interaction with leukocytes; and

(3) assessing (A2) platelet/leukocyte interaction or detecting the presence of a condition causing the platelet/leukocyte interaction or for determining whether a subject has a predisposition for a condition causing platelet/leukocyte interaction involving:

(i) contacting a whole blood or blood-derived sample with (I) or (II) in the presence of an oscillating or rotating magnetic field, and

(ii) monitoring movement of the magnetic particles in response to the oscillating or rotating magnetic field, to determine the presence or absence of platelet/leukocyte interaction function and/or the level of platelet/leukocyte interaction in the whole blood or blood derived sample.

USE - For detecting conditions causing platelet/leukocyte interaction including cerebral vascular accidents, transient ischemic attack, unstable angina, coronary artery disease, acute myocardial infarction and inflammation (all claimed).

ADVANTAGE - The methods provide a fast, reliable point-of-care assessment of platelet/leukocyte interaction. The methods can be performed in wet and dry chemistry format.

Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: B04-B04D2; B04-G01; B04-N06; B05-A03; B05-B02C; B11-C07A4; B11-C07A6;
B12-K04A2

TECH UPTX: 20020725

TECHNOLOGY FOCUS - BIOLOGY - Preferred Ligands: (L1) is a plasma protein, plasma protein fragment, extracellular matrix protein and/or extracellular matrix protein fragment (preferably a component (C1) selected from von Willebrand factor, fibrinogen, fibronectin, Factor II, Factor IIa, Factor V, Factor Va, Factor VIII, Factor VIIIa, Factor IX, Factor IXa, Factor X, Factor Xa, Factor XI, Factor XIa, Factor XII, Factor XIIa, Factor XIII, Factor XIIIa, collagen, vitronectin, laminin, osteopontin, fibrillin, chondroitin sulfate or heparin sulfate, a fragment of proteins and/or leukocyte selective antibody). (L1) is attached to the microparticles covalently, through passive adsorption or through binding to bridging molecules. The plasma protein fragments or extracellular protein fragments are prepared by formation of peptides, formation of peptide mimetics or formation of peptide mimotopes either through recombinant technology or enzymatic cleavage or by linkage of amino acids by non-enzymatic chemical method. (L2) or (L3) and the first ligand of (II) are selected from (C1) or its active fragment (preferably von Willebrand factor or its active fragment). The second ligand of (II) is selected from (C1) or its active fragment (preferably leukocyte selective antibodies, VCAM-1, fibronectin, laminin, ICAM-1, ICAM-2, ICAM-3, collagen osteopontin, vWF, vitronectin, thrombospondin, mucosal addressin cell adhesion molecule 1 (MadCAM-1), P-selectin, L-selectin or E-selectin). The first and the second ligand of (II) are bound to the magnetic or non-magnetic particles. Preferred Microparticles: The microparticles are of irregular, regular or spherical shape and are selected from pollen or microorganisms. Preferred Sample: The whole blood or blood-derived sample (preferably whole blood sample) is an anticoagulated or unanticoagulated whole blood, cells contained within the buffy coat or blood product collected for transfusion purposes or is a sample obtained from a mammal (preferably human) that is undergoing or is about to undergo a course of treatment with a therapeutic agent which affects platelet/leukocyte interaction. The blood product collected for

transfusion purposes is additionally subjected to at least one procedure designed to isolate specific blood components selected from random donor platelets, apheresis platelets, buffy coat or packed red cells. The whole blood or blood-derived sample is placed in contact with an artificial surface, *in vivo* or *ex vivo*, or *in vitro*, prior to use in the method.

Preferred Method: (A1) further involves determining the extent of platelet/leukocyte interaction of several combined suspensions, each comprising a sample obtained from a mammal at a present time interval prior to or during the course of treatment in order to assess platelet/leukocyte interaction during treatment and thus monitor the efficacy of treatment. The step (a) further involves combining the whole blood or blood-derived sample and the solid-phase stimulus with at least one agent that affect platelet/leukocyte interaction for a selected time period and determining the extent of platelet/leukocyte interaction prior to and after addition of at least one agent. The step (3i) occurs in the presence of a rotating magnetic field at a frequency of 2000 - 2500 revolutions per minute (rpm). The step (3ii) is performed by detecting and/or quantitating the difference in concentration of the leukocyte marker compound in the sample after coagulation of the sample.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The microparticles are selected from polystyrene, latex, teflon or polycarbonate.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The microparticles are selected from glass, silica, iron oxide, non-magnetic metals, paramagnetic iron oxide, gold, platinum or palladium.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The microparticles are selected from acrylonitrile, carboxylate, dextran, agarose, nylon or acrylamide. (II) further comprises a leukocyte marker compound (preferably a fluorescent compound). Preferred Method: The step (a) is performed by stirring, shaking, aspiration, application of electromagnetic fields, ultrasound and/or shear. The step (b) is performed by flow cytometry, cell counting, microscopy, photo-microscopy, transmission electron microscopy, scanning electron microscopy, confocal microscopy, video microscopy, enzyme-linked immuno-sorbant assay, radio-immunoassay, immuno-radiometric assay, gel exclusion chromatography, affinity chromatography, histochemical analysis, immuno-chemical analysis, polymerase chain reaction, fluorescence *in-situ* hybridization, southern blotting, western blotting, laser-scanning cytometry, turbidity measurement, aggregometry, intra-cellular ion flux measurement, extracellular ion flux measurement, measurement of cellular releasates, measurement of solid-phase-stimulus/platelet/leukocyte aggregate size, measurement of rate of formation of solid-phase-stimulus/platelet/leukocyte complexes and latex bead agglutination.

ABEX

UPTX: 20020725

EXAMPLE - Whole blood from a healthy volunteer was drawn into a citrate vacutainer tube, an EDTA vacutainer tube and a heparin vacutainer tube. A drop of blood from each tube was added to the reaction well of three separate reaction cards containing a mixture of VWF-coated polystyrene beads and VWF-coated paramagnetic iron oxide particles (VWF-PIOP) and the suspension mixed vigorously for 5 minutes. Aliquots of whole blood (5 lambda) were removed from each card for microscopic wet-mount observation (phase contrast) and stained smear (Hema-3 stain, Fisher Scientific) evaluation. Weak platelet adhesion to the VWF beads were noted with the EDTA blood, with the vast majority of platelets left unbound. Platelets did not associate with VWF-PIOP in the EDTA blood. Both the citrate blood and the heparin blood samples showed extensive binding of platelets to VWF beads with subsequent binding of VWF-PIOP to form large complexes. Few platelets were left unbound. Binding of leukocytes to (or within) these large VWF bead/platelet/VWF-PIOP complexes was not observed either by wet mount or stained smear. Leukocytes and platelets in complex were observed to be associated with the von Willebrand factor coated microspheres and VWF-PIOP in the citrate and heparin samples only when the platelets

displayed hyperactivity or when the platelets and/or leukocytes were subjected to mechanical stress such as repeated centrifugation (800xg, 10 minutes). Mechanical stress did not augment platelet association with the VWF Beads or VWF-PIOP, nor did it promote leukocyte/platelet complex formation in the EDTA blood sample. A test card was prepared as follows: Into a test card such as that in Oberhardt according to US5110727, having a reaction chamber of approximately 30 microl, was placed a reagent composition containing the above noted magnetic and non-magnetic particles coated with vWF, in amounts such that the reagent composition comprises coated PIOP particles (1 - 2 mg/ml and polystyrene particles (from 2 x 10 to the power of 6 to 8 x 10 to the power of 6 per ml). Also placed into the reaction chamber was a leukocyte marker, such as FITC-labeled anti-CD4S, to provide a detectable signal. Once the reaction chamber was filled, the sample was then frozen and lyophilized. A platelet/leukocyte interaction test was carried out as follows: a disposable or test card containing the reagents described above was placed on a platform above a rotating magnet. Whole blood (or other blood-derived) sample was added to a well, which was pulled by capillary action into the reaction chamber. At that time the magnetic particles and non-magnetic particles were freed, with the magnetic particles forming a rotating ring around the central portion of the reaction chamber. As the reaction progressed, the inner edge of the rotating ring migrated toward the center, with the final endpoint providing a full collapse of the inner edge to the central point to form a disc or dot. The total time elapsed was approximately 1 - 20 (preferably 2 - 4) minutes. When the above noted vWF coated PIOP and vWF coated polystyrene particles were used, the presence of platelet/leukocyte interaction was determined by detection of a leukocyte marker present in the original reagent formulation. Alternatively, if the PIOP were coated with a leukocyte ligand (instead of vWF) the occurrence of the platelet/leukocyte interaction was detected by collapse of the PIOP ring itself.

L30 ANSWER 2 OF 7 WPIX (C) 2003 THOMSON DERWENT
 AN 2002-114190 [15] WPIX
 DNN N2002-085175
 TI Platelet function assay reagent for use to perform platelet function assay, comprises magnetic and non-magnetic particles that have sufficient amounts of ligand that directly interact with glycoprotein receptors.
 DC S03
 IN MAHAN, D E; STEWART, M W; MAHAN, D
 PA (PHAR-N) PHARMANETICS INC
 CYC 97
 PI WO 2001086248 A2 20011115 (200215)* EN 31p G01N000-00
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TR TZ UG ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU
 SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
 AU 2001061020 A 20011120 (200219) G01N000-00
 EP 1280931 A2 20030205 (200310) EN C12Q001-56
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 NO 2002005300 A 20030107 (200317) G01N033-53
 ADT WO 2001086248 A2 WO 2001-US11760 20010509; AU 2001061020 A AU 2001-61020
 20010509; EP 1280931 A2 EP 2001-934872 20010509, WO 2001-US11760 20010509;
 NO 2002005300 A WO 2001-US11760 20010509, NO 2002-5300 20021105
 FDT AU 2001061020 A Based on WO 200186248; EP 1280931 A2 Based on WO 200186248
 PRAI US 2000-202638P 20000509
 IC ICM C12Q001-56; G01N000-00; G01N033-53
 AB WO 200186248 A UPAB: 20020306
 NOVELTY - Platelet function assay reagent comprises a mixture of magnetic and non-magnetic particles. There is bound to an outer surface of the

magnetic particles an amount of a first ligand having an affinity for direct interaction with GP-Ib receptors on blood platelets. There is bound to the nonmagnetic particles on an outer surface an amount of a second ligand having an affinity for direct interaction with GP-Ib receptors on blood platelets. Interaction of either of the first and second ligands with the GP-Ib platelet receptor will activate the blood platelets towards aggregation, wherein the first and second ligands can be the same or different.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is for a platelet function assay method.

USE - Perform platelet function assay.

ADVANTAGE - It provides a fast and reliable point-of-care assessment of platelet function.

DESCRIPTION OF DRAWING(S) - The drawing shows a paramagnetic iron oxide particle ring formed during the assay using a rotating magnetic field.

Dwg.1A/4

FS

EPI

FA

AB; GI

MC

EPI: S03-E04E; S03-E13D; S03-E14H1; S03-E14H4

L30 ANSWER 3 OF 7 WPIX (C) 2003 THOMSON DERWENT

AN 2000-182007 [16] WPIX

DNN N2000-134357 DNC C2000-056797

TI Fluorescence spectroscopic determination of biological marker containing bound lanthanide ions for determining e.g. antibodies in solution.

DC B04 C07 D16 E19 J04 K08 S03

IN BOBROW, M N; CODY, M R; MULLINAX, T R

PA (NENL-N) NEN LIFE SCI INC; (NENL-N) NEN LIFE SCI PROD INC

CYC 19

PI WO 9966333 A1 19991223 (200016)* EN 39p G01N033-58
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

US 6030840 A 20000229 (200018) G01N033-20

ADT WO 9966333 A1 WO 1999-US13368 19990615; US 6030840 A US 1998-94628
19980615

PRAI US 1998-94628 19980615

IC ICM G01N033-20; G01N033-58

AB WO 9966333 A UPAB: 20000330

NOVELTY - Spectroscopic determination of chelated lanthanide metal ions bound to marker.

DETAILED DESCRIPTION - Spectroscopic determination of chelated lanthanide metal ions bound to a marker comprises:

(1) contacting chelated lanthanide metal ions bound to a marker with a buffered solution comprising a detergent, an enhancer reagent and a polyanion, in which the buffer maintains the pH of the solution at 3.5-11.5 and the polyanion is present in a concentration so that the lanthanide metal ions disassociate from the marker and reassociate with the enhancer reagent, to transfer the lanthanide metal ions into a highly fluorescent form and

(2) determining the amount of lanthanide metal ion liberated from the marker as a measure of the amount of marker present in the solution by subjecting the solution to a short radiation pulse and detecting the fluorescence of the lanthanide metal ion after the fluorescence from any background source has ceased.

An INDEPENDENT CLAIM is included for a composition comprising lanthanide metal ion, a polyanion comprising at least two acid functional groups derived from carbon, phosphorus, nitrogen and/or sulfur, and an enhancer reagent.

ACTIVITY - Diagnosis-Gen.

5 mu l of streptavidin-Eu (diluted so that 5 mu l gives 100000 cpm when enhanced) were added to microplate wells in triplicate with 195 mu l of a selected enhancement solution, the solutions containing varying

concentrations of a polyanion enhancer component (citrate, phosphonoformate, oxalate or sulfosuccinate). After 30 minutes incubation at room temperature, the plate was read on a DELFIA 1234 time resolved fluorimeter. The highest reading for each curve was taken as 100%. All enhancement solutions contained 20 mu M naphthoyl trifluoroacetone, 50 mu M trioctyl-phosphine oxide and 0.1% Triton X-100 plus the polyanion at the selected concentration. The citrate-based enhancer was used at pH 7.25, the phosphono formate-based enhancer was used at pH 5.6, the oxalate-based enhancer was used at pH 7 and the sulfosuccinate-based enhancer was used at pH 4.2. The results are shown in the figure.

MECHANISM OF ACTION - Fluorescence.

USE - The method can be used for determining the amount of a biological material present in a sample. The method can be used to determine the presence and amount of biological materials in solution, such as antibodies, antigens, DNA fragments, enzymes, hormones, other proteins and other substances naturally present in human or animal body fluids.

ADVANTAGE - The method is advantageous in that it allows for the rapid and complete dissociation of the **lanthanide** metal ion from the chelate complex and subsequent rapid reassociation with the enhancer reagent. Measurement of the resulting fluorescence of the **lanthanide** metal ion thus can be determined quickly (within 5-30 minutes) and with a high accuracy and fluorescent intensity.

DESCRIPTION OF DRAWING(S) - The figure shows the results of incubating streptavidin-Eu (diluted so that 5 mu l gives 100000 cpm when enhanced) added to microplate wells in triplicate with 195 mu l of a selected enhancement solution containing varying concentrations of a polyanion enhancer component (citrate, phosphonoformate, oxalate or sulfosuccinate).

Dwg.3/4

FS

CPI EPI

FA

AB; GI; DCN

MC

CPI: B04-B04C; B04-G01; B04-J01; B04-L01; B04-N02; **B05-A03B**; B05-B01P; B10-A09B; B10-C02; B10-C04B; B10-F02; B11-C07A5; B11-C07B3; B12-K04A; C04-B04C; C04-G01; C04-J01; C04-L01; C04-N02; **C05-A03B**; C05-B01P; C10-A09B; C10-C02; C10-C04B; C10-F02; C11-C07A5; C11-C07B3; C12-K04A; **D05-H09**; **E05-P**; E11-Q03C; J04-C; K09-B

EPI: S03-E14H

TECH

UPTX: 20000330

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred method: The polyanion comprises at least two acid functional groups derived from carbon, phosphorus, nitrogen and/or sulfur and is preferably of formula (I). R1, R3 = OPO3H2, NO2, SO3H, NO, PO3H2, COOH or SH; R2 = optional group, which when present, is 1-10C alkyl (optionally substituted by OH, COOH, NH2, SH, OPO3H2, NO2, acetamido or SO3H), 4-10C cycloalkyl (optionally containing N, O and/or S and optionally substituted by OH, COOH, NH2, acetate, SH, OPO3H2, NO2 or SO3H), 2-6C linear chain characterized by one or more double bonds between 2 adjacent carbons (optionally substituted by OH, COOH, NH2, keto, acetate, SH, OPO3H2, NO2 or SO3H), phenyl, benzyl or pyridyl (optionally substituted by OH, keto, COOH, NH2, SH, OPO3H2, SO3H or NO2) or (CH2)_m-X-(CH2)_n (optionally alkyl substituted by OH, COOH, NH2, SH, acetamido, OPO3H2 or SO3H); m, n = 0-10;

X = CO, PO4H, phenyl, benzyl, pyridinyl, N, S or O (optionally substituted by OH, COOH, NH2, SH, OPO3H2, NO2, Cl, CH3, (CH2)_yNH2, (CH2)_zCH3, keto, phenyl, benzyl, pyridyl, acetamido or SO3H) and y, z = 1-10.

The polyanion especially comprises a citrate, sulfosuccinate, oxalate, dinitrobenzoate, phosphonoformate or pyrophosphate.

The **lanthanide** metal is chelated with a chelating agent which forms a complex with the **lanthanide** metal ion and has a formation constant K of 1011 to 1025. The enhancer reagent comprises a

beta-diketone. The detergent comprises TRITON, TWEEN, NP-40, GAB, zwittergent, Brij or lauryl sulfate.

The enhancer agent also comprises a Lewis base preferably trioctylphosphine oxide. The polyanion comprises 50-120 mM oxalate and the enhancer reagent comprises 10-50 micro-M beta-NTA; or the polyanion comprises 20-60 micro-M phosphonoformate and the enhancer reagent comprises 10-50 micro-M beta-NTA; or the polyanion comprises 5-10 mM pyrophosphate and the enhancer reagent comprises 10-50 micro-M beta-NTA; or the polyanion comprises 10-20 mM citrate and the enhancer reagent comprises 10-50 micro-M beta-NTA; or the polyanion comprises 50-150 mM sulfosuccinate and the enhancer reagent comprises 10-50 micro-M beta-NTA. The enhancer reagent also comprises 50-400 micro-M trioctylphosphine oxide.

The buffer comprises Tris, borate, MOPS, imidazole, PIPES, carbonate or MES. The **lanthanide** metal ion is a europium, terbium, dysprosium or samarium ion. The polyanion has a maximum formation constant K_f of 1011 with the **lanthanide**. The pH of the solution is maintained at 3.8-10 (preferably 4-8).

ABEX

UPTX: 20000330

SPECIFIC COMPOUNDS - The polyanion comprises 1,2-cyclohexane dicarboxylic acid, 1,3,5-cyclohexane tricarboxylic acid, isocitric acid, oxalic acid, pyromellitic acid, 2,4-dinitrobenzoate or nitroterephthalate. The chelating agent comprises diethylene triamine pentaacetate, N-hydroxy-ethylenediamino triacetate, nitriloacetate or 1,4,7,10-tetraazacyclododecane. The beta-diketone comprises 2-naphthyltrifluoroacetone (2-NTA), thenoyl-trifluoroacetone, benzoyl trifluoroacetone or 1,1,1,2,2-pentafluoro-6,6-dimethyl-3,5-heptanedione.

L30 ANSWER 4 OF 7 WPIX (C) 2003 THOMSON DERWENT
 AN 1998-496001 [42] WPIX
 DNN N1998-387364 DNC C1998-149516
 TI Detection of analytes in test samples - using diagnostic neodymium(III), ytterbium(III) or erbium(III) ion-ligand complexes.
 DC B04 D16 J04 S03
 IN HOFSTRAAT, J W
 PA (ALKU) AKZO NOBEL NV; (HOFS-I) HOFSTRAAT J W
 CYC 82
 PI WO 9839654 A1 19980911 (199842)* EN 27p G01N033-533
 RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA
 PT SD SE SZ UG ZW
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
 GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
 MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
 US UZ VN YU ZW
 AU 9868284 A 19980922 (199908) G01N033-533
 EP 968424 A1 20000105 (200006) EN G01N033-533
 R: AT BE CH DE DK ES FI FR GB IE IT LI NL
 US 2002187563 A1 20021212 (200301) G01N033-543
 ADT WO 9839654 A1 WO 1998-EP1287 19980228; AU 9868284 A AU 1998-68284
 19980228; EP 968424 A1 EP 1998-913667 19980228, WO 1998-EP1287 19980228;
 US 2002187563 A1 WO 1998-EP1287 19980228, US 1999-380336 19991123
 FDT AU 9868284 A Based on WO 9839654; EP 968424 A1 Based on WO 9839654
 PRAI US 1997-42354P 19970324; EP 1997-200615 19970303
 IC ICM G01N033-533; G01N033-543
 AB WO 9839654 A UPAB: 19981021
 Detection of an analyte in a test sample comprises a specific binding reaction between the analyte, a specific binding partner for the analyte and an immuno-reactant or a reactant provided with a label. The label is a **lanthanide** ion-ligand complex. The **lanthanide** ion is Nd³⁺, Yb³⁺ or Er³⁺. The ligand comprises, or is in contact with, a sensitising moiety which absorbs in the 400-1,000 (especially 400-800) nm region.

Also claimed is a kit for detection of an analyte in a test sample,

comprising:

(a) a specific binding partner for the analyte, and
 (b) an immuno-reactant or a reactant provided with a label. The label is as described above. The specific binding partner and the labelled immuno-reactant are optionally attached to a carrier.

USE - The process may be used for detection of analytes in test samples, e.g. body fluids or tissues of animal, bacterial or vegetable origin. It may be used for detection of analytes such as antigens, antibodies, (glyco)proteins, peptides, oligonucleotides, nucleic acids, enzymes, haptens or polysaccharides.

ADVANTAGE - The **lanthanide** ion complexes make use of inexpensive 400-1000 nm lasers or other light sources, emit luminescence in the near-IR spectrum, have long luminescence lifetimes, high sensitivity, and good stability with respect to the irradiated light and towards the solvents used, especially towards aqueous solutions.

Dwg.0/0

FS CPI EPI
 FA AB; DCN
 MC CPI: B05-A03B; B11-C07A5; B11-C07B4; B12-K04;
 D05-H09; D05-H10; J04-C04
 EPI: S03-E14H4

L30 ANSWER 5 OF 7 WPIX (C) 2003 THOMSON DERWENT
 AN 1997-450611 [42] WPIX
 DNN N1997-375412 DNC C1997-143782
 TI New fluorescent compounds and their **lanthanide** ion complexes - used as labelling reagents in immunoassays..
 DC B04 B05 D16 E19 J04 S03
 IN MATSUMOTO, K; YUAN, J
 PA (MATS-I) MATSUMOTO K; (SUZM) SUZUKI MOTOR CORP; (SUZM) SUZUKI KK
 CYC 10
 PI EP 794174 A2 19970910 (199742)* EN 15p C07C309-86
 R: CH DE FI FR GB LI SE
 JP 09241233 A 19970916 (199747) 20p C07C309-86
 CA 2187690 A 19970909 (199815) C07C309-86
 EP 794174 A3 19971119 (199816) C07C309-86
 US 5859297 A 19990112 (199910) C07C035-08
 CA 2289220 A1 19970909 (200023) EN C07C309-86
 CA 2289221 A1 19970909 (200023) EN C07C309-86
 EP 794174 B1 20000614 (200033) EN C07C309-86
 R: CH DE FI FR GB LI SE
 DE 69608878 E 20000720 (200041) C07C309-86
 US 6166251 A 20001226 (200103) C07C035-08
 ADT EP 794174 A2 EP 1996-116690 19961017; JP 09241233 A JP 1996-51185
 19960308; CA 2187690 A CA 1996-2187690 19961011; EP 794174 A3 EP
 1996-116690 19961017; US 5859297 A US 1996-735517 19961023; CA 2289220 A1
 Div ex CA 1996-2187690 19961011, CA 1996-2289220 19961011; CA 2289221 A1
 Div ex CA 1996-2187690 19961011, CA 1996-2289221 19961011; EP 794174 B1 EP
 1996-116690 19961017; DE 69608878 E DE 1996-608878 19961017, EP
 1996-116690 19961017; US 6166251 A Div ex US 1996-735517 19961023, US
 1998-223873 19981231
 FDT DE 69608878 E Based on EP 794174; US 6166251 A Div ex US 5859297
 PRAI JP 1996-51185 19960308
 REP 1.Jnl.Ref; EP 354847; EP 493745; JP 02088968; JP 04244085; JP 07010819; WO
 9005916
 IC ICM C07C035-08; C07C309-86
 ICS C07C049-813; C07C331-00; C07D307-91; C07D333-04; C07D333-52;
 C07D333-74; C07D333-76; C07D409-02; C07F005-00; C09K011-06;
 G01N033-533
 AB EP 794174 A UPAB: 19971125
 A fluorescent compound of formula (I) or (II) is new. R = a group capable
 of combining with proteins; n = a whole number.
 Also new are complexes of (I) or (II) with a lanthanoid metal ion.

USE - (I) and their complexes with the lanthanoid metal ion are used as labelling agents in immunoassays.

ADVANTAGE - The labelling reagents of (I) and their complexes have high fluorescence intensities, are cheaper than aromatic amine type labelling reagents, give high synthesis yield, permit both solid-phase and liquid-phase measurements, require less measuring steps to obtain results rapidly and can be synthesized in a stable form permitting long-term storage.

Dwg.0/3

FS CPI EPI

FA AB; GI; DCN

MC CPI: **B05-A03B**; B06-H; B07-H; B10-A02; B10-A09B; B10-A10;
B10-A14; B10-A20; B10-A25; B10-B04A; B10-C04B; B10-F02;
B12-K04; D05-H09; E05-P; E10-A09B1;

E10-F02A2; J04-B01B

EPI: S03-E14H4

L30 ANSWER 6 OF 7 WPIX (C) 2003 THOMSON DERWENT

AN 1995-035612 [05] WPIX

DNN N1995-028159

TI Diagnostics instrument for clinical analysis - includes processing station and carousel holding test packs contg. disposable packs of reagent and impact resistant trays.

DC S03

IN BATE, E; KEARNEY, K R; KELLARD, S; MAHAN, D E; ROBINSON, D;
SHIMEI, T M; WATSON, M; SHIMEL, T M

PA (STAD) AMOCO CORP

CYC 5

PI	US 5374395	A 19941220 (199505)*	48p	G01N021-24
	DE 4436470	A1 19950420 (199521)	50p	G01N035-02
	FR 2711242	A1 19950421 (199521)		G01N035-02
	GB 2283318	A 19950503 (199521)	123p	G01N035-02
	IT 1270130	B 19970428 (199745)		G01N000-00

ADT US 5374395 A US 1993-136654 19931014; DE 4436470 A1 DE 1994-4436470
19941012; FR 2711242 A1 FR 1994-12239 19941013; GB 2283318 A GB 1994-20220
19941006; IT 1270130 B IT 1994-MI2083 19941012

PRAI US 1993-136654 19931014

IC ICM G01N000-00; G01N021-24; G01N035-02

ICS G01N033-16; G01N033-53; G01N033-68

AB US 5374395 A UPAB: 19950207

The automated diagnostics instrument has a special processing station assembly comprising a movable saddle assembly which rides upon and engages the test packs. The movable saddle assembly expresses and mixes reagents with samples in the test packs to form optically detectable analytes and separates and seals waste portions of the samples from the analytes and waste pouches of the test packs. The saddle assembly pref. includes a roller subassembly, a shoe and mixer subassembly, with a sealer subassembly operatively connected to each other.

The roller subassembly mixes reagents and samples in the reaction area of the test packs and moves the background material comprising waste portions of the samples to waste pouches in the test packs. The shoe and mixing subassembly manipulate and mix reagents in blisters and test packs and break the blisters to express reagents from the blisters to the reaction areas of the test packs. The sealer subassembly seals empty reagent blisters, vacated reaction areas and filled waste pouches in the test packs. Pref. the processing station assembly also includes a clamp plate assembly to hold and support the test packs in an erect position.

USE - Automated diagnostics instrument and process for analysing samples in a test pack for an analyte, eg. for detection of infectious organisms.

Dwg.7/50

FS EPI

FA AB; GI

MC EPI: S03-E14H; S03-E14H4; S03-E15

L30 ANSWER 7 OF 7 WPIX (C) 2003 THOMSON DERWENT

AN 1966-11541F [00] WPIX

TI Lanthanide complexes.

DC B00

PA (RICT) RICHTER GEDEON VEGYESZETI GYAR

CYC 3

PI FR 2322 M 19640309 (196800)*

DE 1242629 B (196801)

FR 1479206 A (196801)

NL 136637 B (197241)

PRAI HU 1961-224 19610415

AB FR 2322 M UPAB: 19930831

Water soluble complexes of the rare earth metals with organic molecules which contain at least 2 and pref. at least 3 OH, COOH, and/or SO₃H groups, but no basic groups. For each metal atom there can be complexed 1,2, or 3 molecules of the organic component.

Metals used are La, Ce, Pr, Nd, Sa, Eu, Gd, Tb, Dy, Ho, Er, Yb, Tm, and Lu. Organic components are for example pyrocatechin disulphonic and sulphosalicylic acids.

Anticoagulant and antiphlogistic agents of low toxicity

and

good water solubility.

FS CPI

FA AB

MC CPI: B05-A03; B10-A09; B10-C02; B10-C03; B10-C04; B12-D08; B12-H02

=> d all abeq tech abex tot

L46 ANSWER 1 OF 6 WPIX (C) 2003 THOMSON DERWENT

AN 2002-691469 [74] WPIX

DNN N2002-545563 DNC C2002-195334

TI Determination of concentration of at least one analyte in a test sample involves mixing the sample with a single reagent, irradiating the mixture and calculating the concentration of the analyte.

DC B04 S03

IN SUNDREHAGEN, E

PA (SUND-I) SUNDREHAGEN E

CYC 99

PI WO 2002044721 A1 20020606 (200274)* EN 78p G01N033-53

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ

NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK

DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR

KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT

RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZM ZW

AU 2002023166 A 20020611 (200274) G01N033-53

ADT WO 2002044721 A1 WO 2001-NO480 20011130; AU 2002023166 A AU 2002-23166 20011130

FDT AU 2002023166 A Based on WO 200244721

PRAI NO 2000-6130 20001201

IC ICM G01N033-53

ICA G01N033-533; G01N033-542; G01N033-68

AB WO 200244721 A UPAB: 20021118

NOVELTY - Determination of concentration of at least one analyte in a test sample or an aliquot of a test sample of a complex biological fluid involves mixing the sample or aliquot of the sample with one single reagent to form a mixture, irradiating the mixture with polarized light, measuring the polarization of the emitted light and calculating the

concentration of the analyte.

DETAILED DESCRIPTION - Determination of concentration of at least one analyte in a test sample or an aliquot of a test sample of a complex biological fluid involves:

- (i) mixing the sample or aliquot of the sample with one single reagent such as a solid, solution or premixed solution to form a mixture
- (ii) irradiating the mixture with polarized light which permits the excitation of the fluorescent molecules
- (iii) measuring the polarization of the emitted light, and
- (iv) calculating the concentration(s) of the analyte(s).

The reagent is provided in one single container or compartment of a container and no other reagent is added during the performance of the method. The reagent further comprises at least one type of binding molecule with specific affinity for at least one of the analytes and either fluorescent moieties covalently linked to the binding molecules or fluorescent analogs, fluorescent fragments or fluorescent derivatives of the analyte(s).

INDEPENDENT CLAIMS are also included for:

(1) A reagent for carrying out the method comprising at least one type of binding molecule with specific affinity for at least one of the analyte. The reagent further comprises fluorescent moieties covalently linked to the binding molecules or fluorescent analogs, fluorescent fragments or fluorescent derivatives of the analyte(s); and

(2) Kit for carrying out the method comprising at least one container. The container(s) or compartment of the container(s) contains one single reagent, preferably in a fluidal state. The reagent comprises at least one fluorescence-labeled specific binding molecules towards the analyte(s) to be measured or a fluorescence-labeled analog or fluorescent fragment or fluorescent derivative of the analyte(s) as well as device for obtaining the extract volume(s) of the complex biological fluid to be tested and that is needed in order to perform the method adequately.

USE - For the determination of concentration of at least one analyte in a test sample or an aliquot of a test sample of a complex biological fluid, particularly for the determination of concentrations of clinically related substances in samples of biological material from living organism (claimed) e.g. plants, insects, birds and animals such as mammals (e.g. primates or humans).

ADVANTAGE - The method involves use of stable, durable reagents; is carried out in very few (preferably just one single container); does not require any significant pipette work. The method can be carried out on blood tests after or with simultaneous lysis of the blood cells. The method is a sensitive specific measurement method. The method is carried out at constant temperature by use of correction algorithms empirically generated by temperature's influence on test solutions with known concentration of the analyte.

Dwg.0/8

FS

CPI EPI

FA

AB; DCN

MC

CPI: B04-B04B; B04-B04D; B04-B04G; B04-C01; B04-F04; B04-G01; B04-N04;
B05-A03B; B06-A01; B06-A03; B06-D01; B06-E05; B10-B01B

EPI: S03-E04B5; S03-E04D; S03-E14H1; S03-E14H4; S03-E14H9

TECH

UPTX: 20021118

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Reagent: The reagent is used for each analyte comprising immunocomplexes between an antibody or an immunoactive fragment of an antibody with specific affinity for the analyte(s) and their fluorescent analogs, fluorescent fragments or fluorescent derivatives or is used for an analyte comprising complexes between an aptamer or another synthetic binder with a specific affinity for the analyte and fluorescent analogs, fluorescent fragments or fluorescent derivatives of the analyte(s). The reagent comprises binding molecules with specific affinity for at least one analyte and with fluorescent moieties with absorption between 600 - 1000 (preferably above 620, especially above 640) nm, covalently linked to the binding molecules;

fluorescent binding molecules with specific affinity for one analyte or comprising fluorescent analogue, fluorescent fragments or fluorescent derivative of one analyte only; and different fluorescent moieties covalently bound to different binding molecules with different specific affinities. The reagent with fluorescent residue has maximum coefficient of absorption at a wavelength of above 640 nm. The reagent comprises cell lysing substance or anticoagulant or detergent. The sample material or its aliquot is constituted by a biological material or is constituted by dilution, extraction, dissolution or filtration a dilution or an extract or is dissolved or is filtrated from the biological material. The binding molecule is a peptide, synthetic binder or aptamer composition and is optionally identified by combinatory chemistry technique or phase display or nucleic acid selection technology. The reagent comprises at least one peptide or its derivative with specific binding affinity for an analyte. The binding peptide has fluorescent residue, which is covalently linked and is constituted by less than 30 (preferably less than 20, especially less than 15) amino acids. The peptide or its derivative contains amino acid sequence Ala-Arg-Asn-Arg-Asn or Ala-Arg-Asn-Gly-Asn for quantitation of C-reactive protein. The fluorescent moiety is fluoresceine, Texas Red, Cy5, other Cy Dye FluorLink substance, other Cyanin derivatives, Rhodamin, methyl rhodamin, Biodypi 630/650-X/MeOH, Biodypi 650/655-X/MeOH, Biodypi FL/MeOH, Biodypi R6G/MeOH, Biodypi TMR-X/MeOH Biodypi TR-X/MeOH or other substance from the Biodypi group of substances, Alex Fluor Dyes of different wavelengths, Ruthenium ligand complexes, lanthanoid elements such as Europium, Samarium or Terbium complex bound to chelating ligands such as DTPA, EDTA or N1. The reagent is used in concentrated or dry form or is diluted or reconstituted before use. The reagent is divided between different compartments for combination into one reagent prior to use.

Preferred Process: The polarization of the emitted light is measured as a function of time, either as a continuous kinetic reading or a reading of the change in polarization of the emitted light between two or more points or as a measurement of the polarization of the emitted light after a defined point of time. The method involves the use of standards or calibrators comprising known concentrations of the analyte(s). The concentration of the analyte(s) in unknown samples is calculated by interpolation of the values obtained from the unknown samples on the standard curve obtained from the known standards or calibrators. The standard curve is stored in an artificial memory, optionally connected to the fluorescent polarization instrument in use. The method is carried out using temperature correction algorithms, either generated empirically or theoretically. These algorithms compensate for differences in fluorescence polarization caused by the differences in temperature at different time of measurement of standards and unknown samples, or between standards or between unknown samples.

Preferred Kit: The reagent contained in a container or a compartment of the container is formed to a ready-to-use reagent by mixing the content from different containers before or immediately before or in connection with the execution of the analysis.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Sample Material: The sample material or its aliquot is constituted by blood, blood serum, blood plasma, blood cell, lysate from blood or blood cell, urine, cerebrospinal fluid, tear fluid, sputum, semen, plasma, semen or material aspirated from the gastrointestinal tract or feces, extract or filtrate of suspension of feces, plant material or its extract or dissolved plant material or its filtrate.

ABEX

UPTX: 20021118

EXAMPLE - An assay reagent was prepared by making buffer of (150 mM) sodium chloride (100 mM) phosphate, pH 7.4. To this buffer (2 mg/ml) bovine gamma globulin was added and Triton X-100 to a final concentration of 0.1 v/v%. Cy5-labeled Tyr-Trp-Ala-Asn-Phe-Ala-Arg-Asn-Arg-Asn (1×10^{-11} mole/ml) was added and optionally a bacterostatic agent like sodium azide (0.01%) was added for prolonged storage. Aliquots of this mixture were placed in separate containers and combined with unknown blood samples or

aliquots of blood samples. For determination of C-reactive protein, an aliquot of the whole blood sample was taken and combined with the assay reagent in the separate container. The separate containers were kept at a temperature of 32degreesC. The container was shaken and the blood flew out of the capillary. The cells were lysed by the assay reagent. The C-reactive protein of the test sample aliquot reacted with Cy5-labeled Tyr-Trp-Ala-Asn-Phe-Ala-Arg-Asn-Arg-Asn of the assay reagent. After shaking, the container was placed in the fluorescence polarization at 32degreesC. The mixture in the container was irradiated with polarized light of 650 nm wavelength. The concentration of C-reaction protein of the unknown sample was calculated by interpolation of the polarization value of the emitted light. It was observed that with mild bacterial infection, the content of C-reactive protein of sample (20 ul) was 10 - 100 mg/l. Each C-reactive protein molecule reacted with five molecules of Cys5-labeled Tyr-Trp-Ala-Asn-Phe-Ala-Arg-Asn-Arg-Asn. The concentration of Cys5-labeled Tyr-Trp-Ala-Asn-Phe-Ala-Arg-Asn-Arg-Asn was thus adjusted compared to the blood volume to be combined with the assay reagent.

L46 ANSWER 2 OF 6 WPIX (C) 2003 THOMSON DERWENT
 AN 2002-489927 [52] WPIX
 DNN N2002-387327 DNC C2002-139068
 TI Novel reagent useful for assessment of hemostatic potential of blood or plasma sample, comprises a coagulation activator.
 DC B04 D16 P31
 IN BAGLIN, T; DOOBAY, H; FISCHER, T J; LUDDINGTON, R; TEJIDOR, L
 PA (ALKU) AKZO NOBEL NV
 CYC 97
 PI WO 2002034109 A2 20020502 (200252)* EN 44p A61B000-00
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TR TZ UG ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO
 RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
 AU 2002015382 A 20020506 (200257) A61B000-00
 ADT WO 2002034109 A2 WO 2001-US32563 20011018; AU 2002015382 A AU 2002-15382
 20011018
 FDT AU 2002015382 A Based on WO 200234109
 PRAI US 2000-698589 20001027
 IC ICM A61B000-00
 AB WO 200234109 A UPAB: 20020815
 NOVELTY - A reagent (I) comprising a coagulation activator at a concentration of 11 picomolar or less, for assessment of the hemostatic potential of a blood or plasma sample, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit for assessing the hemostatic potential of a test sample comprising a coagulation activator at a concentration of 11 picomolar or less, or the activator and instructions for diluting the activator, vesicles, a metal divalent cation or a metal salt capable of dissociating into a metal divalent cation, instructions for adding the activator, metal cation or metal salt and vesicles to a test sample, and instructions for assessing the hemostatic potential of the test sample.

USE - The reagent and the kit are useful for indicating a sample to be hypocoagulable, normal or hypercoagulable, depending upon the condition of the patient from which the sample was taken, for indicating a patient to have thrombotic tendency, hemorrhagic tendency, or stasis, and also for assessing hemostatic potential of a blood or plasma sample (claimed). (I) is useful in the drug discovery and drug development processes by modifying the components or concentrations of the reagent. (I) is useful to determine the amount of plasma to be modified in order to restore coagulability to normal.

ADVANTAGE - The reagent allows for globally assessing both the hypercoagulable potential and hypocoagulable potential of a patient in a

single assay, which is accurate, sensitive and easy. The test is simple and can be automated on standard laboratory coagulometers. The test is based on the rate of fibrin polymerization which allows detection of perturbances in the propagation, amplification and polymerization pathways, whereas in the traditional prothrombin time test, these parts of the coagulation pathway are overshadowed by the excessive amounts of Factor IIa produced by the initiation phase.

Dwg.0/10

FS CPI GMPI

FA AB; DCN

MC CPI: B04-B04D4; B04-B04D5; B04-H19; B04-N02;
B05-A01B; B05-A03A; B05-B01P; B05-C07; B11-C08E; B12-K04A;
D05-H09

TECH UPTX: 20020815

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Reagent: (I) further comprises vesicles or liposomes. The vesicles comprise platelets, cellular debris, phospholipid vesicles (prepared by dilution, sonication, dialysis or extrusion), or platelet microparticles. The coagulation activator comprises tissue factor which is a recombinant or purified, truncated tissue factor, or cells expressing tissue factor on their surface. The tissue factor comprises a metal cation, especially a divalent metal cation such as magnesium, calcium or manganese or metal salt (5-50, preferably 15-35 mM), preferably a halide of magnesium, calcium or manganese, which dissociates into a metal cation. The tissue factor is at a concentration of 11, 8 or 6 picomolars, preferably 3 picomolars or less. The vesicles comprise phospholipids (at a concentration of 10-300 micromolar, preferably 50-200 micromolar) which comprise one or more of phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine at a ratio of 0-10, preferably 10 %, by mole phosphatidylserine, 5-30, preferably 20 %, by mole phosphatidylethanolamine and the remainder, preferably 70 %, by mole phosphatidylcholine. The coagulation activator comprises tissue factor-rich mammalian tissue extracts, tissue factor purified from mammalian tissue or thromboplastin. The coagulation activator is capable of detecting defects in the initiation phase. (I) further comprises an activator of an anticoagulant pathway, preferably an activator of protein C which is a purified human or non-human mammalian **thrombomodulin**, soluble or membrane associated **thrombomodulin**, native **thrombomodulin** or **thrombomodulin** reconstituted with phospholipids, partially or fully glycosylated **thrombomodulin**, and fully deglycosylated **thrombomodulin**. The protein C activator (**thrombomodulin**) is at a concentration of 30 nanomolar or less, preferably 5-20 nanomolar. The **thrombomodulin** comprises heparin or heparin-like molecules and is relipidated with phospholipids comprising 10 % phosphatidylethanolamine. (I) further comprises buffers and/or stabilizers, or phospholipids.

Preferred Kit: The kit further comprises calcium cation or calcium salt that dissociates into a calcium cation, and an activator of an anticoagulant pathway and instruction for adding the activator to the test sample. The **thrombomodulin** is provided separately from the coagulation activator, and mixed with heparin, heparin sulfate or heparin-like molecules. The kit has a first container having the coagulation activator which is a tissue factor at a concentration of 11 picomolars or less mixed with vesicles which are phospholipids at a concentration of 10-300 picomolar, a second container having a metal salt at a concentration of 5-50 mM, and third container having the coagulation activator mixed with vesicles and an activator of an anticoagulant pathway which is **thrombomodulin** at a concentration of 300 nanomolar or less.

ABEX UPTX: 20020815

EXAMPLE - An assay was conducted for detecting the coagulability, by adding 50 micro-l of plasma to 50 micro-l of the activator and 50 micro-l of the start reagent which consisted of 0.25 M calcium chloride. A normal

sample, a hypocoagulable sample (factor VIII deficient plasma) and a hypercoagulable plasma (protein S deficient plasma) were evaluated at various dilutions of the activator. The activator was diluted with a buffer at two dilutions, 1:100 and 1:50000 of its original concentration. The assay was conducted at 37 degrees C, and the reaction was monitored at 580 nm for 300 seconds. Endpoints were calculated for time and rate indices of clot formation. The ratio of the endpoint of reagent dilution (x) for specimen/endpoint of reagent dilution (y) for specimen to the endpoint of reagent dilution (x) for npp/endpoint of reagent dilution (y) for npp was calculated, where x is 1:100 dilution and y is a series of dilutions. The results were expressed as the magnitude of deviation at a given dilution or as the dilution required to deviate from ideal (normal value or normal range). As the dilution of the reagent was greater (y became larger) the results for the two abnormal plasmas (the hypercoagulable and hypocoagulable plasmas) tested began to deviate from the calculated endpoints or ratios of the normal plasma. The hypocoagulable specimen produced ratios that were greater than 1 and the hypercoagulable specimen had ratios that were less than 1 for the endpoint (clot time)/ratio combination.

L46 ANSWER 3 OF 6 WPIX (C) 2003 THOMSON DERWENT
 AN 2001-420624 [45] WPIX
 DNN N2001-311623 DNC C2001-127360
 TI A method and a composition for the treatment of blood.
 DC B04 P31 S03
 PA (ASAHI ASAHI KASEI KOGYO KK
 CYC 1
 PI JP 2001083144 A 20010330 (200145)* 10p G01N033-48
 ADT JP 2001083144 A JP 1999-256245 19990909
 PRAI JP 1999-256245 19990909
 IC ICM G01N033-48
 ICS A61B005-15
 AB JP2001083144 A UPAB: 20010813
 NOVELTY - A method for determination of reactions of blood cells.
 DETAILED DESCRIPTION - A method for treatment of blood for cell reaction, particularly a mediator releasing reaction, particularly histamine, leukotriene, platelet activating factor (PAF) or cytokine by addition of a chelating agent, particularly ethylenediamine tetraacetic acid (EDTA), citric acid and/or oxalic acid, an anticoagulant without chelating activity, particularly heparin, plasmin, a protease, an azo dye, hirudin, dicumarol, **thrombomodulin**, an antibody to blood coagulation factor and/or a receptor which binds with the blood coagulation factor, and a metal salt, particularly chlorides, sulfates, carbonates, nitrates and/or phosphates, capable of dissolution of bivalent cation, particularly Ca, Mg, Mn, Zn, Cd and/or Cu, in an aqueous medium.
 USE - Determination of reaction of blood cells in immune and allergic reaction.
 ADVANTAGE - Determination of blood cell functions with satisfactory reproducibility without separation of blood cells.
 Dwg.0/0
 FS CPI EPI GMPI
 FA AB; DCN
 MC CPI: B04-B04D5; B04-C02; B04-G01; B04-H06; B04-L05C; B05-A01B;
 B05-C04; B05-C05; B05-C07; B06-A01; B10-C02; B12-K04A
 EPI: S03-E14H
 TECH UPTX: 20010813
 TECHNOLOGY FOCUS - BIOLOGY - Treatment of blood cells.
 ABEX UPTX: 20010813
 EXAMPLE - A blood sample of a healthy volunteer was treated with the claimed process and 7.8-8.0 % of coefficient of variation (CV) was obtained.

AN 1999-571846 [48] WPIX
 DN N 1999-421410 DNC C1999-166879
 TI New assays for determination of activity of components in the Protein C anticoagulant pathway, used for the study of diseases such as deep venous thrombosis and pulmonary embolism.
 DC B04 D16 S03
 IN HALL, C M Y; ROSEN, B S
 PA (CHRO-N) CHROMOGENIX AB; (INLI) INSTRUMENTATION LAB SPA; (HALL-I) HALL C M Y; (ROSE-I) ROSEN B S
 CYC 85
 PI WO 9947699 A1 19990923 (199948)* EN 66p C12Q001-56
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
 OA PT SD SE SL SZ UG ZW
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD
 GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV
 MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
 UA UG UZ VN YU ZW
 EP 947585 A1 19991006 (199948) EN C12Q001-56
 R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO
 SE SI
 AU 9930339 A 19991011 (200008) C12Q001-56
 EP 947585 B1 20010725 (200143) EN C12Q001-56
 R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 DE 69801210 E 20010830 (200158) C12Q001-56
 ES 2162361 T3 20011216 (200206) C12Q001-56
 US 6395501 B1 20020528 (200243) C12Q001-56
 US 2002115127 A1 20020822 (200258) C12Q001-56
 NZ 506747 A 20030328 (200325) C12Q001-56
 ADT WO 9947699 A1 WO 1999-EP1599 19990311; EP 947585 A1 EP 1998-105043
 19980319; AU 9930339 A AU 1999-30339 19990311; EP 947585 B1 EP 1998-105043
 19980319; DE 69801210 E DE 1998-601210 19980319, EP 1998-105043 19980319;
 ES 2162361 T3 EP 1998-105043 19980319; US 6395501 B1 US 1999-273413
 19990319; US 2002115127 A1 Cont of US 1999-273413 19990319, US 2002-50441
 20020116; NZ 506747 A NZ 1999-506747 19990311, WO 1999-EP1599 19990311
 FDT AU 9930339 A Based on WO 9947699; DE 69801210 E Based on EP 947585; ES
 2162361 T3 Based on EP 947585; NZ 506747 A Based on WO 9947699
 PRAI EP 1998-105043 19980319
 IC ICM C12Q001-56
 ICS G01N033-86
 AB WO 9947699 A UPAB: 19991122
 NOVELTY - New assays for the determination of activity of components in the Protein C anticoagulant pathway uses additional metal ions to improve the sensitivity of the assays.
 DETAILED DESCRIPTION - (A) A novel in vitro photometric method for qualitative screening and quantitative determination of the functional activity of components of the Protein C anticoagulant pathway of blood coagulation, comprises measuring the conversion rate of an exogenous substrate by an enzyme. The activity of the enzyme is related to the Protein C anticoagulant activity, in a blood sample of a human comprising coagulation factors and the exogenous substrate after at least partial activation of coagulation through the intrinsic, extrinsic, or common pathway and triggering coagulation by:
 (1) adding calcium ions, and
 (2) comparing the conversion rate with the conversion rate of a normal human blood sample determined in the same way, characterized by adding further metal(s) ions selected from divalent metal ions and monovalent copper ions to the sample.
 INDEPENDENT CLAIMS are also included for the following:
 (1) a kit for use in methods as in (A) comprising:
 (a) an activator for the Protein C; or exogenous activated Protein C or exogenous Protein C together with an activator of Protein C;
 (b) suitable coagulation activator;
 (c) an exogenous synthetic substrate for either Factor Xa or thrombin

comprising a photometrically measurable leaving group;

- (d) calcium ions; and
- (e) further metal(s) ions; and optionally
- (f) coagulation factors; in separate containers and/or in containers comprising mixtures of at least two of the components in aqueous solution or in lyophilized form, and

(2) a reagent for use in methods as in (A) characterized by comprising the further metal(s) ions and at least one of the components as in (1a)-(1d) or (1f) in one container in aqueous solution or in lyophilized form.

USE - The methods can be used for the global screening for defects in the Protein C anticoagulant pathway of blood coagulation, for determination of free Protein S activity in a blood sample, for determination of Protein C activity in a blood sample, and for screening for Factor V mutations in a blood sample (claimed). They allow improved screening and diagnosing of defects in the Protein C anticoagulant pathway in investigation of patients with thromboembolic diseases such as deep venous thrombosis and/or pulmonary embolism.

ADVANTAGE - The addition of further metal ions in the presence of calcium ions enhances the anticoagulant activity of the Protein C anticoagulant pathway and provides for a high resolution between different levels of Protein C activity and Protein S activity, respectively, and a high discrimination for the presence of the FV:Q506 mutation, resulting in an improved sensitivity and specificity for detection of defects in components of the Protein C anticoagulant pathway with photometric and/or clotting methods.

Dwg.0/8

FS CPI EPI

FA AB; DCN

MC CPI: B04-B04D5; B04-C01A; B04-C01B; B04-H19; B04-L01; B04-N04; B05-A01B;
B05-A03; B11-C07B2; B11-C08E3; B11-C09; B12-K04A; B12-K04A2; B14-F04;
B14-F08; D05-H09

EPI: S03-E14H

TECH UPTX: 19991122

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Ion: The metal ions may be e.g. Mg²⁺, Mn²⁺, Zn²⁺, Cu²⁺, Ni²⁺, Sr²⁺ and/or Cu⁺.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Protein: The protein C may be activated using a snake venom enzyme e.g. Protac (RTM) or thrombin optionally with **thrombomodulin**. Coagulation may also be activated using e.g. ellagic acid, collagen or silica. The medium may also contain a fibrin polymerization inhibitor e.g. Gly-Pro-Arg-Pro. The methods may also comprise use of a photometric substrate comprising a p-nitroaniline group (pNA) as a chromophoric leaving group, a naphthylamine or coumarine derivative group as a fluorophoric leaving group, or an isoluminolamide group as a luminophoric leaving group. The substrate for Factor Xa may be e.g. benzoyl-Ile-Glu-Gly-Arg-pNA , N-a-Z-D-Arg-Gly-Arg-pNA, CH₃SO₂-D-Leu-Gly-Arg-pNA, or MeO-CO-D-CHG-Gly-Arg-pNA. The substrate for thrombin may be e.g. H-D-Phe-Pip-Arg-pNA, pyroGlu-Pro-Arg-pNA, H-D-Ala-Pro-Arg-pNA, Z-D-Arg-Sarc-Arg-pNA, AcOH-H-D-CHG-But-Arg-pNA, or H-D-HHT-Ala-Arg-pNA.

ABEX UPTX: 19991122

EXAMPLE - The effect of manganese and magnesium ions on the determination of Protein C activity in a 3-stage chromogenic thrombin generation assay using the Protein C activation Protac C (RTM) was carried out using the following components: Samples: Protein C deficient plasma with and without addition of purified human Proteinc C to yield 0, 0.1, 0.5 and 1.0 IU/ml of Protein C; Sample dilution: 1:41 in 25 mmol/L Tris-HCl pH 7.6, 20 mmol/L NaCl, 0.2% BSA; Protein C activator: Protac C (RTM) was used as a stock solution containing 10 U/ml. Final concentration during activation of Protein C = 0.17 U/ml. Mg²⁺ and Mn²⁺ ions were added to yield final concentrations during activation of Protein C of 0.4 and 0.04 mmol/L respectively. Reagent 1: Bovine Factor IXa, 180 pmol/L; Reagent 2:

Phospholipids (a mixture of purified phospholipids containing 43% phosphatidylcholine, 27% phosphatidylserine and 30% sphingomyelin), 60 μmol/L Gly-Pro-Arg-Pro, 0.36 mg/ml (polymerization inhibitor) Human Factor V, 0.2 U/ml; Chromogenic thrombin substrate: S-2796, 2 mmol/L. The assay was carried out as a 3-stage method comprising, in the first stage, combining 50 μl of diluted plasma with 50 μl of Protein C activator Protac C (RTM) and incubating this mixture for 3 minutes at 37°C, whereafter coagulation was achieved by adding 50 μl of Reagent 1 and 50 μl of Reagent 2 and incubating the mixture for 5 minutes at 37°C, whereafter, in the third stage, the substrate hydrolysis was carried out by adding 50 μl of the chromogenic thrombin substrate S-2796 and incubating for 4 minutes at 37°C. The reaction was then terminated by lowering the pH through addition of 50 μl of 20% acetic acid. The optical density (OD) of the samples in the microwells was then recorded at 405 and 490 nm and the difference in OD between 405 and 490 nm was calculated. The results showed that by including manganese and magnesium ions in a reaction system containing calcium ions, a strong enhancement of the anticoagulant activity was obtained, manifested by the fact that increasing concentrations of Protein C in the samples resulted in a much decreased absorbance, i.e. a much decreased thrombin generation. In contrast, in the presence of calcium ions alone, there was a much lower resolution in absorbance, i.e. in thrombin generation, at increasing Protein C concentrations. Thus, the addition of further metal ions constitutes an improved method for determination of Protein C activity.

L46 ANSWER 5 OF 6 WPIX (C) 2003 THOMSON DERWENT
 AN 1999-494622 [41] WPIX
 DNN N1999-368411 DNC C1999-145093
 TI Measuring coagulant activity assessment in the presence of metal ion.
 DC B04 S03
 IN SPILLERT, C R
 PA (UYNE-N) UNIV NEW JERSEY; (UYNE-N) UNIV NEW JERSEY MEDICINE & DENTISTRY
 CYC 84
 PI WO 9941615 A1 19990819 (199941)* EN 39p G01N033-86
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
 OA PT SD SE SZ UG ZW
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD
 GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LS LT LU LV
 MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
 UA UG UZ VN YU ZW
 AU 9925949 A 19990830 (200003) G01N033-86
 US 6245573 B1 20010612 (200135) G01N033-86
 ADT WO 9941615 A1 WO 1999-US2792 19990209; AU 9925949 A AU 1999-25949
 19990209; US 6245573 B1 US 1998-22449 19980212
 FDT AU 9925949 A Based on WO 9941615
 PRAI US 1998-22449 19980212
 IC ICM G01N033-86
 ICS C12Q001-56
 AB WO 9941615 A UPAB: 19991011
 NOVELTY - A method for analyzing the blood of a mammal to determine the presence or development of pathology related to abnormalities in the coagulation state of the blood of the mammal
 DETAILED DESCRIPTION - Analyzing the blood of a mammal to determine the presence or development of pathology related to abnormalities in the coagulation state of the blood of the mammal, comprises:
 (a) collecting a sample of whole blood from the mammal;
 (b) preparing at least two aliquots of blood from the sample;
 (c) adding at least one metal ion reagent to one of the aliquots;
 (d) measuring the clotting time of the aliquots; and
 (e) correlating the difference in clotting time between the aliquots to the presence or development of abnormalities in the coagulation state of the blood of the mammal.
 INDEPENDENT CLAIMS are also included for:

- (1) a diagnostic kit for carrying out the method above, comprising at least 1 container containing a metal ion reagent; and
- (2) a method for analyzing the blood of a mammal to determine the presence or development of pathology related to abnormalities in the viscosity of the blood of the mammal sequentially comprising
 - (i) collecting a sample of whole blood from the mammal in the presence of an anticoagulant;
 - (ii) preparing at least 2 aliquots of blood from said sample;
 - (iii) adding an amount of at least 1 metal ion reagent to one of the aliquots;
 - (iv) measuring the relative viscosity of the aliquots; and
 - (v) correlating the difference in relative viscosity between the aliquots to the presence or development of abnormalities in the viscosity of the blood of the mammal.

USE - The method is used to assess platelet function in patients and for testing the effect of substances on the platelet function (claimed).

Dwg.0/0

FS CPI EPI

FA AB; DCN

MC CPI: B04-B03B; **B04-B04D2; B04-B04D5;** B04-B04G;
B04-C01; B04-F05; B04-H01; B04-L04; B04-L05C; B04-N02; B04-N04;
B05-A01B; B05-A02; B05-A03B; B05-B02C; B10-B02D; B10-C04E; B11-C08E;
B12-K04A

EPI: S03-E14H

TECH UPTX: 19991105

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Materials: The metal ion reagent is a solution comprising a salt of a metal selected from the group consisting of silver, mercury, lead, cadmium, barium, copper, tin, tungstate and/or selenate. The metal ion reagent is a solution of a silver salt, especially silver nitrate. Alternatively, the metal ion reagent is a solution of a mercuric salt, especially mercuric chloride.

Preferred Method: The sample of blood of step (a) is collected in the presence of a calcium-binding anticoagulant, and the measurement of clotting time of step (d) is initiated by the addition of a calcium salt to the aliquots. A modulator of blood coagulation is added to at least one of the aliquots at or prior to step (d). The modulator is selected from tissue factor, prothrombotic venoms, thrombin, ecarin, homocysteine, platelet activating factor, fibrinogen, kaolin, celite, adenosine diphosphate, arachidonic acid, collagen, ristocetin, protein C, protein S, antithrombin III, **thrombomodulin**, tissue plasminogen activator, urokinase, streptokinase, von Willebrand Factor, cancer cell extracts, amniotic fluid and/or therapeutic drugs. The prothrombotic venom is Russells' viper venom.

ABEX UPTX: 19991105

EXAMPLE - The re-calcification time of citrated plasma with citrated whole blood samples from the same patients were evaluated in the absence of mercuric ion (n=12 samples). The plasma re-calcification time was 634 +/- 260 seconds (mean +/- standard deviation), whereas that of whole blood was 426 +/- 131 seconds. The reduced re-calcification time of whole blood versus plasma is attributed to pro-coagulants associated with the cellular portion of blood, principally platelets and monocytes. The effect of mercuric ion on the re-calcification time of plasma and whole blood was evaluated on a different set of patient samples, following the General Methodology above. In citrated whole blood, mercuric ion significantly reduces the re-calcification time when compared to control. However, in plasma, mercuric ion significantly prolongs re-calcification time. Thus, the effect of mercuric ion during the clotting of whole blood is to increase any pro-coagulant effect contributed by the cellular components of the blood. The experiments demonstrated that the cellular components of blood contribute to the pro-coagulant activity of blood and that the addition of mercuric ion further increased the pro-coagulant activity thereby reducing the clotting time.

L46 ANSWER 6 OF 6 WPIX (C) 2003 THOMSON DERWENT
AN 1995-065873 [09] WPIX
DNN N1995-052283 DNC C1995-029233
TI Diagnosing impaired blood flow - by administering contrast agent and generating composite images after two time intervals, difference representing status of arterial blood supply.
DC B05 K08 P31 S03 S05 T01
IN DRANE, W E
PA (UYFL) UNIV FLORIDA
CYC 1
PI US 5377681 A 19950103 (199509)* 14p A61B005-05
ADT US 5377681 A Cont of US 1989-434336 19891113, Cont of US 1992-899227 19920616, US 1994-242708 19940513
PRAI US 1989-434336 19891113; US 1992-899227 19920616; US 1994-242708 19940513
IC ICM A61B005-05
ICS A61B006-00
AB US 5377681 A UPAB: 19950306
Diagnosing impaired blood flow in an organ of a patient comprises administering a non-contrast agent. A first series of parallel two-dimensional images are generated, spatially sepd. along an axis of a major blood supply to the organ at a first time sufficient to allow the agent to be extracted to the organ. The images are added together on a pixel-by-pixel basis to generate a two-dimensional first composite image which represents total contrast agent uptake at the first time. A second series of similar images are generated after a second time when there is a detectable decrease of contrast agent. A second composite image is created representing agent retention at the second time. A third two-dimensional composite image is generated by subtracting the second from the first composite images. This represents reagent washout between the two times, indicating the status of arterial blood supply along the axis. The third image is displayed.
USE - The method can be used to diagnose impaired organ, esp. heart or brain, blood flow using in vivo imaging technology.
ADVANTAGE - The non-invasive method is esp. useful in patients who cannot undergo stress testing due to risk factors.
Dwg.0/4
FS CPI EPI GMPI
FA AB; DCN
MC CPI: B05-A04; B05-B01A; B05-B02C; B05-C07; B11-C08; B12-K04A2; B12-K07;
K08-E
EPI: **S03-E14H1; S05-D01B1; S05-D02B2; S05-D02C; T01-J06A;**
T01-J10C2